The quest for the theory of human longevity

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Actuaries and gerontologists (scientists who study aging) have some interests in common—members of both professions are interested in whether there are fundamental quantitative laws, which explain human survival up to extreme old ages. This common interest allowed them to share a foundation when they first met at the International Symposium "Living to 100 and Beyond: Survival at Advanced Ages" (January 17–18, 2002, Lake Buena Vista, Florida). This article summarizes our reflections on this interesting meeting and our presentations made there.

Attempts to develop a fundamental quantitative theory of aging, mortality, and life span have deep historical roots. In 1825, the British actuary Benjamin Gompertz discovered a law of mortality, known today as the Gompertz law. Specifically, he found that the force of mortality (known in modern science as mortality rate, hazard rate, or failure rate) increases in geometrical progression with the age of adult humans. According to the Gompertz law, human mortality rates double over about every eight years of adult age. Gompertz also proposed the first mathematical model to explain the exponential increase in mortality rate with age.

The Gompertz law of exponential increase in mortality rates with age is observed in many biological species, including humans, rats, mice, fruit flies, flour beetles, and human lice (see Gavrilov, L.A. & Gavrilova, N.S., *The Biology of Life Span: A Quantitative Approach*, NY: Harwood Academic Publisher, 1991), and, therefore, some general theoretical explanation for this phenomenon is required. Many attempts to provide such theoretical underpinnings for the Gompertz law have been made, and the problem now is to find out which of these theories is correct.

The current situation with applicability of the Gompertz law to extreme old ages is a paradoxical one. On the one hand, it has been well known for a long time that the Gompertz law is not applicable to mortality rates at advanced ages—the observed mortality rates are always lower than predicted by the Gompertz model, and, not surprisingly, the actual number of survivors to extreme ages is always higher than predicted by the Gompertz law. Figure 1 illustrates the mortality deceleration observed at advanced ages contrary to the predictions of the Gompertz law.

It is interesting to note that Gompertz (1825) himself found that at advanced ages mortality rates increase less rapidly than an exponential function, thus forestalling two centuries ago the recent fuss over "late-life mortality deceleration," "mortality leveling off," and "late-life mortality plateaus" (see review in Gavrilov L.A. and Gavrilova N.S., "The reliability theory of aging and longevity." *Journal of Theoretical Biology*, 213: 527-545).

Paradoxically, the Gompertz law and the Gompertz-Makeham law are nevertheless often applied to estimate the oldest-old mortality rates by extrapolation in order to "close" the life tables. When confronted with the question of why these "wrong" formulas are used, the demographers/actuaries usually reply that this is not an important issue, because life expectancy at birth is not very sensitive to how exactly

Figure 1

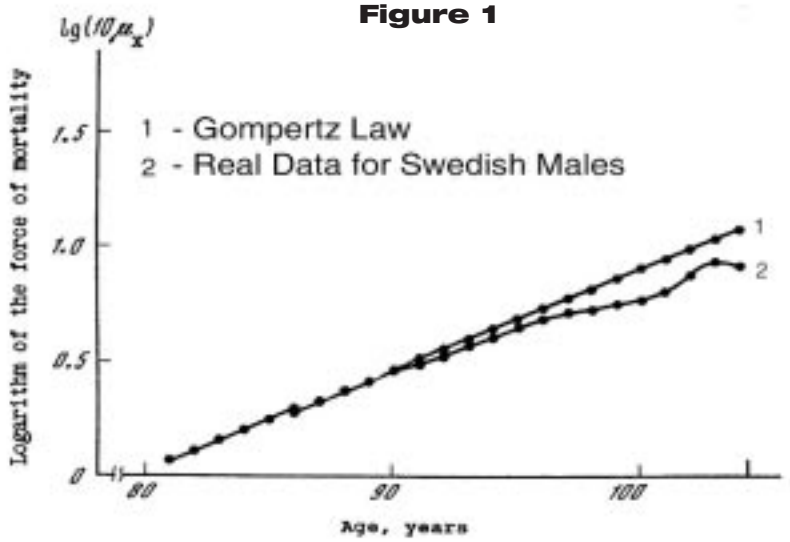

Figure 1. Mortality kinetics at advanced ages for Swedish males.

1 - theoretical dependence corresponding to exponential growth in the force of mortality with age (the Gompertz law with parameters $R = 3.46 \cdot 10^{-5}$ year^{-1} and $\alpha = 0.101$ year^{-1})

2 - real dependence for Swedish males. The statistical data for ages 81-85 are taken from the official Swedish 1956-60 life table, and data for ages 85-100 correspond to mortality in 1945-1967 estimated by the method of extinct generations (Depoid, 1973).

Adapted from: Gavrilov, L.A. & Gavrilova, N.S., *The Biology of Life Span: A Quantitative Approach*, NY: Harwood Academic Publisher, 1991.

the life tables are closed. The same "wrong" formulas and related assumptions are often used for graduation (smoothing procedures) of the mortality trajectories at advanced ages. It is extremely important, therefore, to know exactly how a particular life table was closed and/or graduated, before using it for testing of any statistical models. If the Gompertz or the Gompertz-Makeham laws were already introduced into the data by the method of life table construction/graduation, these data would not be useful for statistical hypothesis testing. Thus, the Gompertz law is known to be not applicable to the oldest-old mortality, unless the data are spoiled by artificial introduction of this law during extrapolation/graduation procedures.

The history of mortality studies at extreme ages is very rich in ideas and findings. In this article we would like to bring your attention to one seminal paper, which was published more than 60 years ago: Greenwood M., Irwin J.O. "Biostatistics of Senility," *Human Biology*, 1939, 11: 1-23. Interestingly, this article was considered to be so important that it was featured on the front page of the journal *Human Biology*.

This study, accomplished by the famous British statistician and epidemiologist, Major Greenwood, may be interesting to discuss again now for two reasons: (1) First, it is devoted to the studies of mortality at extreme ages. The authors of this paper admitted that the topic of their paper had "little actuarial importance" (in 1939), but may be of interest to biologists. However, now, 60 years later, this topic has great actuarial importance, as is evident from the topic of "Living to 100 and Beyond: Survival at Advanced Ages." (2) Second, this 1939 article correctly describes and forestalls the main specific regularities of mortality at advanced ages.

The first important finding was formulated by Greenwood and Irwin in the following way: "**…the increase of mortality rate with age advances at a slackening rate, that nearly all, perhaps all, methods of graduation of the type of Gompertz's formula overstate senile mortality"** (Greenwood, Irwin, 1939, p. 14). This observation is confirmed now and is known as the "late-life mortality deceleration."

The authors also suggested **"the possibility that with advancing age the rate of mortality asymptotes to a finite value"** (Greenwood, Irwin, 1939, p. 14). Their conclusion that mortality at exceptionally high ages follows a first order kinetics (also known as the law of radioactive decay) was confirmed later by other researchers, including A.C. Economos ("Kinetics of metazoan mortality," *J. Social Biol. Struct*. 1980, 3: 317-329), who demonstrated the correctness of this law for humans and laboratory animals. This observation is known now as the "mortality leveling-off" at advanced ages, and as the "late-life mortality plateau." Moreover, Greenwood and Irwin made the first estimates for the asymptotic value of human mortality (one-year probability of death, qx) at extreme ages using data from the life insurance company. According to their estimates, "… **the limiting values of qx are 0.439 for women and 0.544 for men"** (Greenwood and Irwin, 1939, p. 21). It is interesting that these first estimates are very close to estimates obtained later using more numerous and accurate human data including recent data on supercentenarians (those who survive to age 110).

Thus, the force of mortality practically ceases to increase at extreme old ages. The result is that the mortality kinetics of long-lived people is similar to the kinetics of radioactive decay, with a "half-life" corresponding to approximately one year (Gavrilov and Gavrilova, 1991). It is known from mathematics and physics that in this event there can be no absolute life span limit. This simple exponential law of survival at extreme ages allows us to estimate the chances of a centenarian (100 years) to become a supercentenarian (110 years), which is about $(0.5)^{10} = 0.001$. Thus, those countries that have more than 1,000 centenarians in their population, may expect the emergence of supercentenarians. If the numbers of centenarians are higher, persons with ages over 110 years could also be expected.

Greenwood and Irwin also proposed a possible explanation of very slow growth of mortality with age among centenarians. They suggested that very old people were less subjected to external stresses and shocks because they restricted their activities and rarely appeared in public (Greenwood and Irwin, 1939, p.14). Although this explanation could be challenged now, it still deserves some attention as a possible contributing factor to mortality deceleration at advanced ages. It is interesting that the authors also tried to analyze animal mortality at advanced ages and found the same regularities as in humans (Greenwood and Irwin, 1939, p. 21).

Further studies of mortality at advanced ages confirmed the major findings of Greenwood and Irwin (1939). The method of extinct generations proposed by P. Vincent ("La mortalité des vieillards," *Population* 1951, 6:181-204) and developed further by F. Depoid ("La mortalité des grands vieillards," *Population* 1973, 28: 755-792) and V. Kannisto ("On the survival of centenarians and the span of life." Population Studies 1988, 42: 389-406) opened new opportunities for more accurate mortality estimation at extreme ages. The dedicated research work by Väinö Kannisto (1916–2002), who collected a large body of data on mortality at advanced ages and finally created (together with Roger Thatcher), the Kannisto-Thatcher Oldest-Old Database, is of particular importance. More accurate data on human mortality at ages over 100 years allowed researchers to confirm earlier observations that human mortality at advanced ages is growing more slowly than is predicted by the Gompertz law.

The next important question is: why is the Gompertz law not applicable to the oldest-old mortality? As it was already noted, Greenwood and Irwin explained this phenomenon by taking into account

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the more protected environment of very old people. This explanation, however, is not applicable to laboratory animals demonstrating similar deceleration of mortality at advanced ages. A more general explanation of mortality deceleration phenomenon is that it may be the result of population heterogeneity at advanced ages. There is, however, one problem with testing this hypothesis. It may not be difficult to generate the mortality trajectories that will be close to the observed trajectories by assuming that population is a mixture of subgroups of people with different Gompertz parameters. The real problem here is whether there is any sense in such computational exercises. Is there any direct evidence indicating increased population heterogeneity at advanced ages?

The answer to this question is provided in Figure 2. The graph illustrates the dependence of the daughter's life span (expressed as additional years of life gained/lost compared to the reference life span level in the same birth cohort) as a function of maternal life span. For more methodological details of this study, see the original publication (Gavrilova N.S. and Gavrilov L.A. "When does human longevity start?: Demarcation of the boundaries for human longevity". *Journal of Anti-Aging Medicine*, 2001, 4: 115-124). Interestingly, the dependence of the daughter's life span on the maternal life span appears to consist of two lines—one for shorter-lived mothers (deceased prior to age 85) with a very weak dependence of the daughter's life span on the maternal life span, and another, for longer-lived mothers (deceased after age 85), with extremely strong and steep dependence.

Figure 2

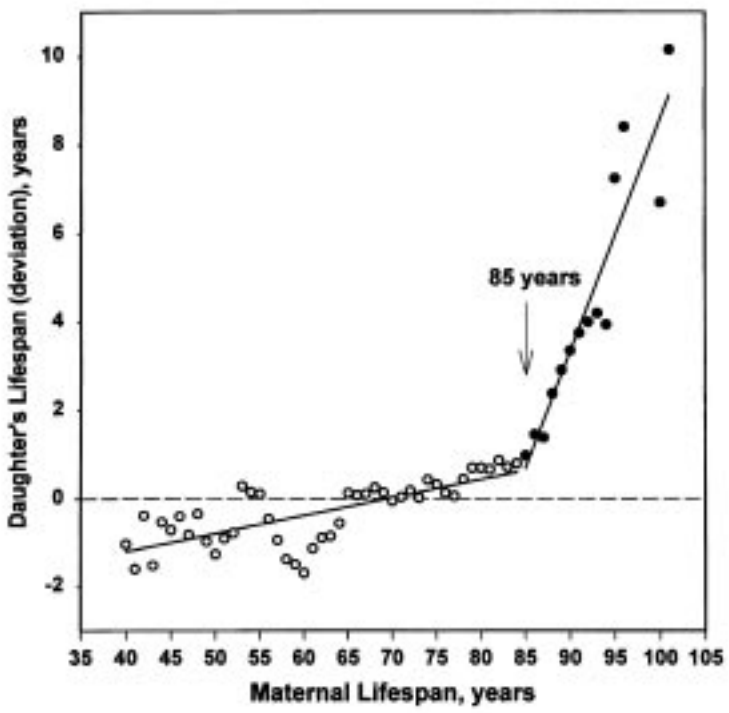

Figure 2. Daughter's life span (deviation from the cohort mean) as a function of *maternal* life span. Based on the data for 5,779 daughters from European aristocratic families born in 1800-1880 and survived by age 30. Data are smoothed by 5-year moving average.

Adapted from: Gavrilova N.S. and Gavrilov L.A. "When does human longevity start?: Demarcation of the boundaries for human longevity". *Journal of Anti-Aging Medicine,* 2001, 4: 115-124.

Daughters born to long-lived mothers may live 10 years longer, on average, if their mother reached age 100. This indicates that long-lived people are fundamentally different from other people in the sense that their children also live significantly longer lives. The breaking point at about age 85 for mothers indicates the age when death becomes much more selective in its timing and when population heterogeneity becomes an important issue. Thus, there is direct evidence for increased population heterogeneity at advanced ages, which may contribute to mortality deceleration in later life. This finding also has an actuarial significance, indicating that maternal life span is predictive for individual life span, if the mother lives beyond age 85.

Reliability theory of aging and mortality

The explanation of late-life mortality deceleration based on population heterogeneity is, however, completely untenable in the case of genetically uniform populations of laboratory animals, as well as technical devices, in which the same regularities are observed to hold as for human beings. Thus, we need to look for even more general explanations of the mortality kinetics at advanced ages. These explanations can be found in terms of reliability theory (see Gavrilov and Gavrilova, 1991; 2001).

Reliability theory is a general theory about systems failure. It allows researchers to predict the age-related failure kinetics for a system of given architecture (reliability structure) and given reliability of its components.

Reliability theory predicts that even those systems that are entirely composed of

non-aging elements (with a constant failure rate) will nevertheless deteriorate (fail more often) with age, if these systems are *redundant* in irreplaceable elements. Aging, therefore, is a direct consequence of systems redundancy. The "actuarial aging rate" (the relative rate of age-related mortality acceleration corresponding to parameter a in the Gompertz law) increases, according to reliability theory, with higher redundancy levels.

Reliability theory also predicts the late-life mortality deceleration with subsequent leveling-off, as well as the late-life mortality plateaus, as an inevitable consequence of *redundancy exhaustion* at extreme old ages. This is a very general prediction of reliability theory: it holds true for systems built of elements connected in parallel, for hierarchical systems of serial blocks with parallel elements, for highly interconnected networks of elements, and for systems with avalanche-like random failures (Gavrilov & Gavrilova, 1991). The reliability theory also predicts that the late-life mortality plateaus will be observed at any level of initial damage: for initially ideal systems, for highly redundant systems replete with defects, and for partially damaged redundant systems with an arbitrary number of initial defects. Furthermore, reliability theory predicts possible *paradoxical mortality decline in late life* (before eventual leveling-off to mortality plateau) if the system is redundant for *non-identical components* with different failure rates. Thus, in those cases when "apparent rejuvenation" is observed (mortality decline among the oldest-old) there is no need to blame data quality or to postulate initial population heterogeneity and "second breath" in centenarians. The late-life mortality decline is an inevitable consequence of *age-induced population heterogeneity* expected even among initially identical individuals, redundant in non-identical system components (Gavrilov & Gavrilova, 2001). Late-life mortality decline was observed in many studies and stimulated interesting debates because of the lack of reasonable explanation. Reliability theory predicts that the late-life mortality decline is an expected scenario of systems failure (Gavrilov & Gavrilova, 2001).

The reliability theory explains why mortality rates increase *exponentially* with age in many adult species (Gompertz law) by taking into account the *initial flaws (defects)* in newly formed systems. It also explains why organisms "prefer" to die according to the Gompertz law, while technical devices usually fail according to the Weibull (power) law. Moreover, the theory provides a sound strategy for handling those cases when the Gompertzian mortality law is not applicable. In this case, the second best choice would be the Weibull law, which is also fundamentally grounded in reliability theory. Theoretical conditions are specified when organisms die according to the Weibull law: organisms should be relatively free of initial flaws and defects. In those cases when none of these two mortality laws is appropriate, reliability theory offers more general failure law applicable to adult and extreme old ages. The Gompertz and the Weibull laws are just special cases of this unifying more general law (Gavrilov, Gavrilova, 2001).

The theory explains why relative differences in mortality rates of compared populations (within a given species) vanish with age, and mortality convergence is observed (known as the compensation law of mortality) due to the exhaustion of initial differences in redundancy levels.

The phenomena of mortality increase with age and the subsequent mortality leveling-off are theoretically predicted to be an inevitable feature of all reliability models that consider aging as a progressive accumulation of random damage (Gavrilov and Gavrilova, 1991; 2001). In short, if the destruction of an organism occurs, not in one, but in two or more, sequential random stages, this is sufficient for the phenomenon of aging (mortality increase) to appear and then to vanish at older ages. Each stage of destruction corresponds to one of the organism's vitally important structures being damaged. In the simplest organisms with unique, critical structures, this damage usually leads to their deaths. Therefore, defects in such organisms do not accumulate, and the organisms themselves do not age, they just die when damaged. In more complex organisms with many vital structures and significant redundancy, every occurrence of damage does not lead to death because of this redundancy. Defects do accumulate, therefore, giving rise to the phenomenon of aging (mortality increase). Thus, aging is a direct consequence (trade-off) of systems redundancy that ensures increased reliability and life span of organisms. As defects accumulate, the redundancy in the number of elements finally disappears. As a result of this redundancy exhaustion, the organism degenerates into a system with no redundancy, that is, a system with elements connected in series, with the result being that any new defect leads to death. In such a state, no further accumulation of damage can be achieved, and the mortality rate levels off.

Overall, reliability theory has an amazing predictive and explanatory power and requires only a few general and realistic assumptions. It offers a promising approach for developing a comprehensive theory of aging and longevity that integrates mathematical methods with biological knowledge, including evolutionary theory and systems repair principles. Reliability theory can be also useful in actuarial practice for predicting human survival up to extreme old ages.

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